



## Review

# Immunophysiology versus immunopathology: Natural autoimmunity in human health and disease

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## Abstract

Based on the analysis of literature and our own data, some key concepts of natural autoimmunity are reviewed from the point of the Pathophysiology: immunological regulation of homeodynamics, physiological autoimmunity versus autoallergy and predictive roles of natural autoantibodies are discussed. Hypothesis of Immunculus and principle of Immunacea are correlated to some of clinical examples with immunopathological data and the perspectives of autoimmunomics are described.

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## 1. Introduction

Historically, immunology emerged as a branch of applied microbiology. Therefore “microbiological” thinking, namely its idea of war against aliens, has persisted in minds for decades due to the fact that generations of immunologists have been educated by microbiologists. The cells of immune

system were metaphorically interpreted as “gendarmes” or “border guards”; first this allegory was probably coined in 1847 by Virchow [1] and brightly expressed much later (1896) by Duclaux [2]. Nonetheless, let us discuss the situation if the founders of immunology had happened to be physiologists and pathophysiologists (like Ivan Petrovich Pavlov, Walter Bradford Cannon, and others) instead of microbiologists (Louis Pasteur, Paul Ehrlich, and others) and it had been developing within the framework of physiology and pathophysiology?

The immune system probably would have been considered as maintenance of the molecular homeodynamics

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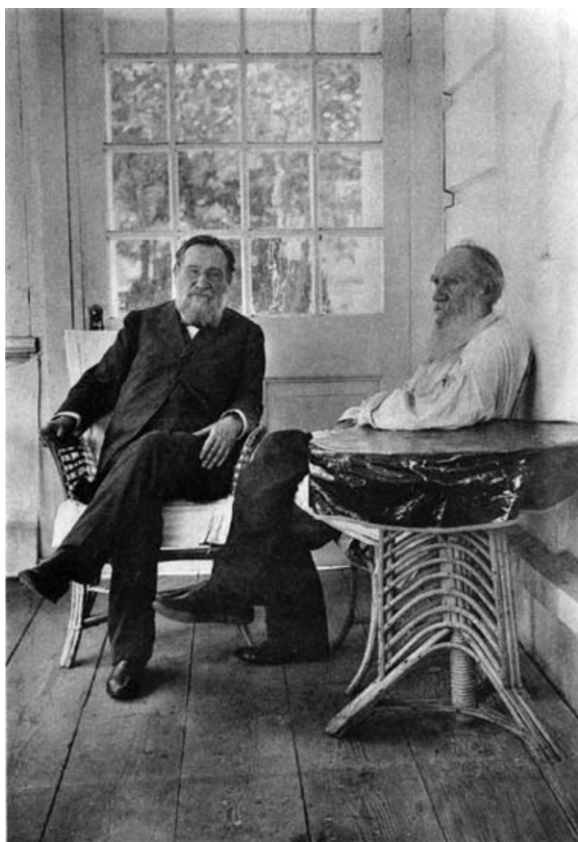


Fig. 1. Founder of physiological autoimmunity concept Ilya I. Metchnikoff (1845–1916) and supporter of preventive medicine ideas L.N. Tolstoy (1828–1910) during conversation. 30th May 1909. “Yasnaya Polyana” estate, photo by S.A. Tolstaya (Bers).

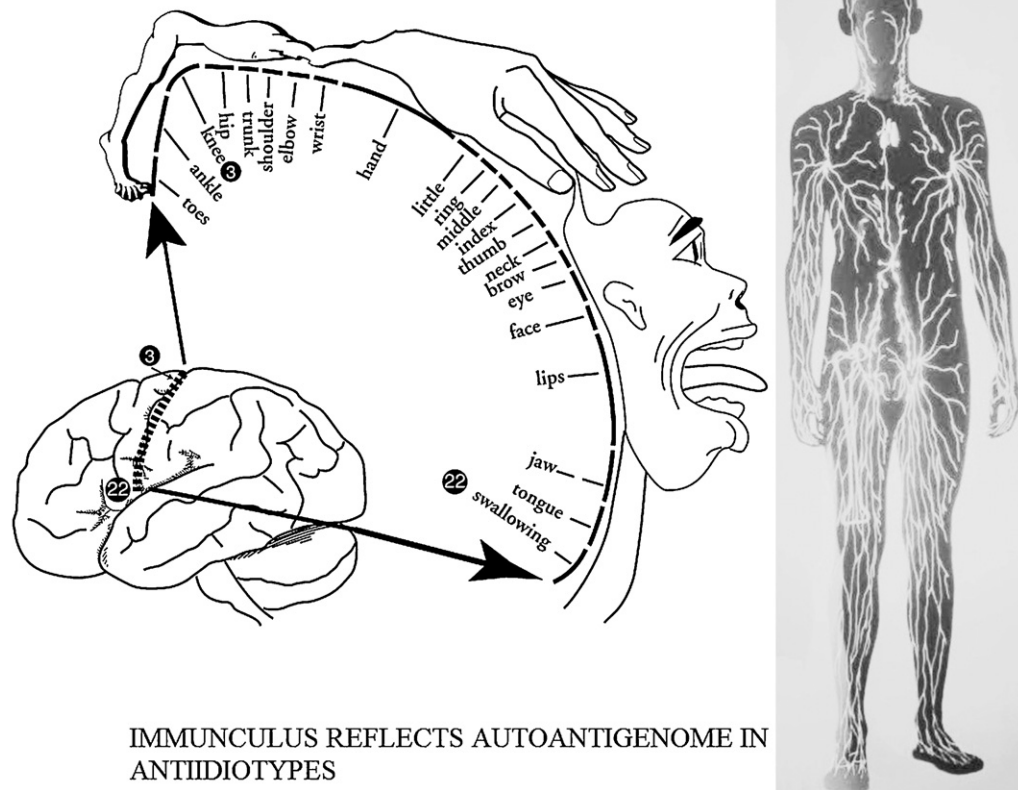
of the whole body, and the terms: “sense of antigenicity”, “immune analyzer”, “immunological image”, “immune reflex” (instead of “secondary immune response”) etc., could have become quite customary from the very beginning, in the same way as “immunological memory” or “immunosynapse” in modern texts. In this case the term “immunity” has been associated not with the metaphor of “alerted guard” involved in permanent war against microbes (which is until now a routine view) but rather a housekeeper of factors challenging for homeodynamics, mostly endogenous in their origin.

Almost 120 years ago Ilya Ilyich Metchnikoff (who put Darwinian logics into the very foundation of his Immunology) (Fig. 1) suggested that the main predestination of the immune system is not “struggle” against non-self, but rather “harmonization of self”, or even ontogenetic creation of multi-cellular organism, in spite of interior contradictions of its elements [3]. Participation of immune cells in permanent host struggle against aliens is just one of the facets of a much wider biological predestination of the immune system which is responsible for the control of dynamic self-maintenance, self-reparation, self-construction and self-optimization of an organism, and perpetual self-harmonization of the primarily imperfect and contradictory body under the conditions of permanent pressure of the environment [4,5].

Metchnikoff prophesied the existence and role of “physiological inflammation” or natural autoimmunity. Unfortunately, his lone voice was not heard at that time, and it was only much later that similar ideas were expressed. For example, Matzinger’s [6] “danger hypothesis” implies that the immune system is not concerned with discrimination and killing of the alien, but it is aimed to identify and block the potentially dangerous. It may serve as grounds for explanation of many previously unexplained phenomena such as: constant presence of abundant “normal” microbial flora (“aliens”!) in each healthy organism and physiological pregnancy, in which any healthy woman is capable to let the development of a semi-allogenic fetus without destroying it, etc. As it was stated by Iwasaki and Medzhitov in their review of relations between innate and adaptive immunity [7], “. . .there are still many fundamental questions that remain poorly understood, . . ., including the mechanisms by which pathogen-specific innate immune recognition activates antigen-specific adaptive immune responses”. In this connection we shall mention a concept recently coined by Marshall and colleagues [8]. According this concept, a great number of microorganisms are able to persist within human cells of a “clinically healthy” individual (their genes forming so called “interactome” with human genome). It is possible because they possess with antagonists of vitamin-D-dependent receptor (VDR), which controls the start of human innate immunity mechanisms. Hence, our cells cannot kill these intracellular germs by means of innate bactericidal effectors and develop adaptive immune responses toward their antigens. The latter are involved in mimicry with self epitopes, which supports the autoantibody production. Disorders of vitamin D metabolism and VDR-depending innate immunity are reported in many autoimmune diseases, as well as in chronic infections. Reactivators of VDR in combination with antibiotics were successfully applied in some chronic autoimmune diseases, such as rheumatoid arthritis and Hashimoto’s autoimmune thyroiditis (AIT) [8–10].

In pathophysiological approach, the systems supervising the growth, development and aging of the whole organism and all its components are supposed to coordinate primarily the sequence and intensity of reading of the genetic information in various cells. This task can be achieved neither by neural mechanisms, nor via hormonal agents, which are involved in accelerating or slowing down the metabolic processes. The neurotransmitters, hormones and their receptors lack ontogenetic and event-driven variability needed for this purpose, while the cells producing them lack the necessary mobility and all-embracing dispersal – the qualities *inherent to the immune system* [11]. Transfer of the emphasis in the main purpose of the immune system from defense to homeodynamic regulation will necessarily lead to re-evaluation of some conventional views, for example, such as the phenomena of physiological autoimmunity and the general role of natural autoantibodies (auto-Abs). In our opinion, it is physiological autoimmunity that provides for bringing-together and co-tuning of genetic information processing in

## PENFIELD'S HOMUNCULUS MAKES BODY IMAGE IN CNS



## IMMUNCULUS REFLECTS AUTOANTIGENOME IN ANTIIDOTYPES

Fig. 2. Immunculus and neurological “Homunculus”: analogy of concepts. Two main regulatory systems operate with 2 principles of body image reflection. Neurological homunculus reflects body structure via activities of neurons in somato-sensory cortical zones and represents for CNS operations an image of the body [12]. Immunculus (Immune Homunculus) of the body consists of clonal mosaics, represented by auto-antiidiotypic antibodies. They form internal immunological images of all autoantigens. Immunculus is used by immune system for physiological self-control of homeodynamics [13–15].

different cells of the holistic “Body” through the complete ontogeny.

## 2. Regulatory autoantibodies, Immunculus and Immunacea effect

Auto-Ab(s) can be regarded as recognizing molecules, bearing in mind that all regulatory processes in the organism are based upon complementary intermolecular recognition. The system of autoimmunity serves as a mirror in dynamic maintenance of individual self-identity, because it is capable of universal inducible reproduction of complementary molecules. This is known, by analogy with Penfield’s somatosensory homunculus, as principle of immune homunculus (Immunculus) [12–15] and illustrated in Fig. 2.

Moreover, the network of idio-anti-idiotypic regulation includes receptors of hormones, autacoids and neurotransmitters, as well as auto-anti-idiotypic Abs to bioregulators, which in turn, are mirror “internal immunological images” of their ligands. By means of production of auto-Abs to any regulatory molecules and their receptors the

immune system may exert influence upon cellular proliferation, differentiation and dying, as well as any other genetically determined events at molecular and cellular levels. For example, specific antibodies against chromatin receptors of endocrine cells penetrate cell nuclei in vitro and in vivo, and influence specific mRNA transcription, DNA replication and production/secretion of hormones [11,13,16–18]. Idiotypic–antiidiotypic mechanisms may cause the appearance of *auto-antiidiotypic antibodies*. Their CDR regions can be stereochemically similar to receptor-binding parts of primary antigens (including hormones, neurotransmitters, autacoids, drugs, etc.). Such *auto-antiidiotypes* could reproduce or antagonize, at least partially, the biologic activity of original bioregulators. Many experimental and clinical data directly witness that phenomena of this kind are real. Antibodies with biological activity similar to hormones, autacoids, enzymes and drugs of different classes have been obtained or registered in patients or healthy donors [11,17–20]. Hypothetically by such anti-idiotypic mechanism *the immune system may reproduce functionally active copies of ANY (!) biologically active molecule*. Is this not something like a realization of an ancient myth about Panacea (Πανάκεια, Panakeia) – all-healing? The term “*effect of*

*Immunacea*” may be proposed as applicable to this potency of immune system [18].

Polyclonal natural human immunoglobulins taken from many donors and admixed can contain a lot of these immunological images, as a kind of collective impact of their individual immunological experiences. Could unique wideness and effectiveness of intravenous immunoglobulin (IVIG) therapy be partially related to the phenomenon of “*Immunacea*”? In our opinion, the effect of *Immunacea* is still underestimated in its application in the treatment of *non-infectious somatic diseases*. Recently, the possibility to model some autoimmune disorders by means of immunization with antibodies toward absent antigen has been shown by Shoenfeld et al. in animals not expressing certain target autoantigens [17]. We predict that the introduction of antibodies against a protein missing in a genetically deficient organism will allow for the immune system to produce its immune analog, which may be a promising approach to treatment of some hereditary diseases [18].

### 3. Clearance function of the immune system

Probably, one of the most important (evolutionary archetypical) homeodynamic functions of the immune system is its involvement in clearance [15,19], a prototype of the immune system eliminating such erratic objects as viruses, bacteria and fungi. It includes the elimination of immune complexes. But, first of all, this function is directed to utilization of permanently emerging debris products from lastingly dying self cells of the body. Many activities of the immune system can be derived from this ancient function.

Starting from classical Metchnikoff’s works it has been assumed that clearance of both endogenous and exogenous products is carried out by macrophages, which express Toll-like receptors (for conservative microbial by-products) and scavenger receptors (for some modified alien or self proteins) [21]. However, this does not explain the whole spectrum of phagocytic clearance. Macrophages do not “sense” via these receptors the vast majority of intact alien and self molecules; neither can they “sense” waste products of self cell apoptosis which must also be utilized. Here we encounter an evident obstacle in the comprehension of clearance mechanisms, because macrophages cannot “notice” most of the targets. Any macrophage per se cannot discriminate a normal serum albumin from a defective one, or a senescent erythrocyte from a young one. Nonetheless, the question as to what the macrophage must gobble and what it should not touch has an effective solution. Phagocytes use specialized signatures (“tags”) attached to items that are to be utilized – namely auto-antibodies [22]. These attach themselves to any product which is to be “gulped down” by macrophages, and, first of all, to waste products of apoptosis or eryptosis [23]. By means of superficial Fc-receptors macrophages are bound to Ab-antigen complexes (soluble as well as particulate ones) and take them up efficiently by receptor endocytosis.

Figuratively speaking, antibodies (opsonins) play the part of scent marks for “blind dogs” (phagocytes) and help them recognize effectively the objects intended for utilization.

### 4. Autoantibodies, cell death, physiological and pathological autoimmunity

*Nota bene:* Production of antibodies is regulated (according to feedback principle) by the quantity of complementary antigens (processed and available for recognition by immunocompetent cells) [24]. That is why any increase of garbage product concentrations is a signal for appropriate raise in the synthesis of specific antibodies, used as signatures for withdrawal of this discharge. Individual rates of apoptosis/replacement of different specialized cells are roughly the same in any healthy adult. Nearly constant level of antigenic waste production under normal conditions is probably the main reason for nearly the same serum levels of various (in terms of specificity) auto-antibodies in each healthy adult individual, practically regardless of sex and age [13,14,19]. On the contrary, pathological changes in heart or lungs, kidneys or liver, and any other organs lead to abnormal increase of “cardiotropic”, “pulmotropic”, “renotropic” or other “organotropic” auto-antibodies [19], because virtually all diseases from the earliest latent onset are accompanied by notable augmentation in the apoptosis rate among certain populations of cells, with more or less massive splash of their specific antigens (Figs. 3 and 4). In Fig. 3 we have superimposed the distribution of the auto-Ab toward several separated by isoelectric focusing cardiac proteins, obtained in 10 healthy donors (thin lines) and in 1 our patient with cardiomyopathy (thick dashed line), thus demonstrating the change of “normal” pattern of autoimmunity to unusual one – in disease. Fig. 4 results from our study of anti-thyroid auto-Ab and thyroid function in 95 Russian families, where at least one of parents has diagnosis AIT, proven clinically and paraclinically according Japanese thyroidological association (JTA) criteria of 2002 [24]. The seemingly healthy children of these parents, still having no established AIT diagnosis and full set of JTA criteria, were compared to *their ill parents* and to 100 healthy children of nearly the same age, *but without AIT in families*. It has been shown that both anti-thyroglobulin (anti-TG) and anti-thyroperoxidase (anti-TPO) autoantibodies, considered to be typical for AIT [24] presented in sera of all 3 groups. But, not only parents with overt AIT manifested significantly higher levels of anti-thyroid autoimmunity, than healthy children. Seemingly healthy children of sick parents had elevation of anti-TPO and anti-TG long before the establishment of overt AIT, and with still normal thyroid function.

The potential triggering roles for anti-thyroid autoimmunity may be attributed to certain infections with cross-specificity of germ and self antigens, or to alternative splicing of thyroglobulin under the influence of different iodine supply in various periods of life [20,22,25].



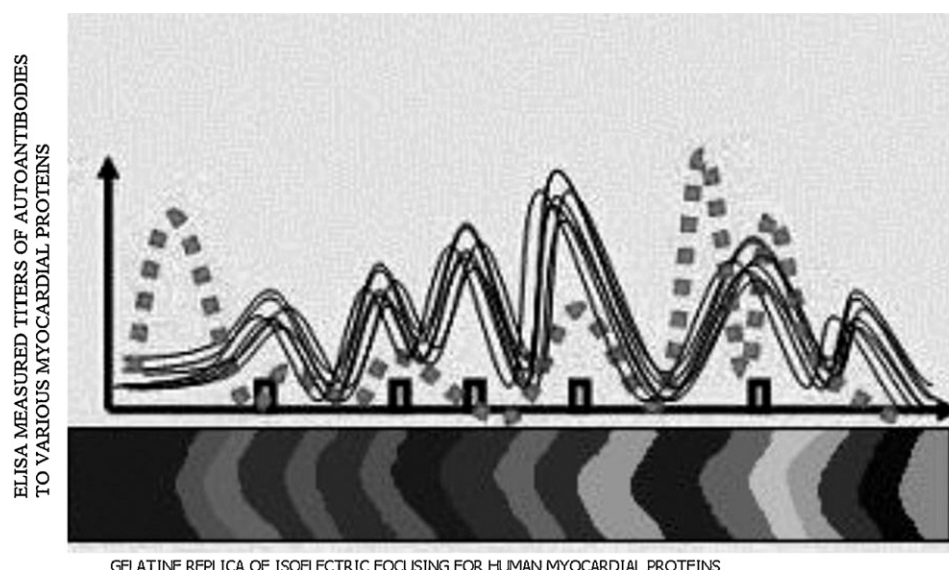


Fig. 3. Cumulated data of cardiotropic autoimmunity in healthy donors (thin lines) and in one case of cardiomyopathy (thick dashed line). Along horizontal axis – isoelectric focusing replica for human myocardial proteins, along vertical axis – levels of autoantibodies toward these antigens, measured by ELISA test. The pattern of sick person differs from typical health pattern of autoimmunity.

In view of Metchnikoff's concept of autoimmune harmonization for phylogeny and ontogeny, among these triggers of autoimmunity one should not forget the phenomenon of spontaneous microchimerism in humans, especially in multiparous women. This has been long ago suggested as principally important reason of AIT, although Lee Nelson appreciated the significance of such microchimerism as a potentially defensive mechanism of normal pregnancy [26,27]. An interesting question, arisen in this connection, is: "Why women live longer than men?" Is gender-connected longevity related not only to freedom from bad habits of men, but also to women's ability to give a new life? Possibly, it depends partly from persistence of fetal cells in maternal

tissues (microchimerism) [28]. But, at the same time prevalence of almost all autoimmune diseases (like AIT) among females is much greater, than in males [29]. In our opinion, anti-idiotypic mechanism may signalize to mother about proper or improper status of fetus via autoimmune images of fetal antigens. Recently we have demonstrated that allogeneic stem cells, at least in parabiotic models, may penetrate into organism of rodents and differentiate into thyrocytes, thus contributing into thyroid regeneration [30]. It is a question, if similar phenomenon takes place in human pregnancy? This has been supposed for cases of perinatal autoimmune thyroid disease [31]. Perhaps, in such mosaics it is autoimmunity which acts in order to harmonize chimerical organism, in full

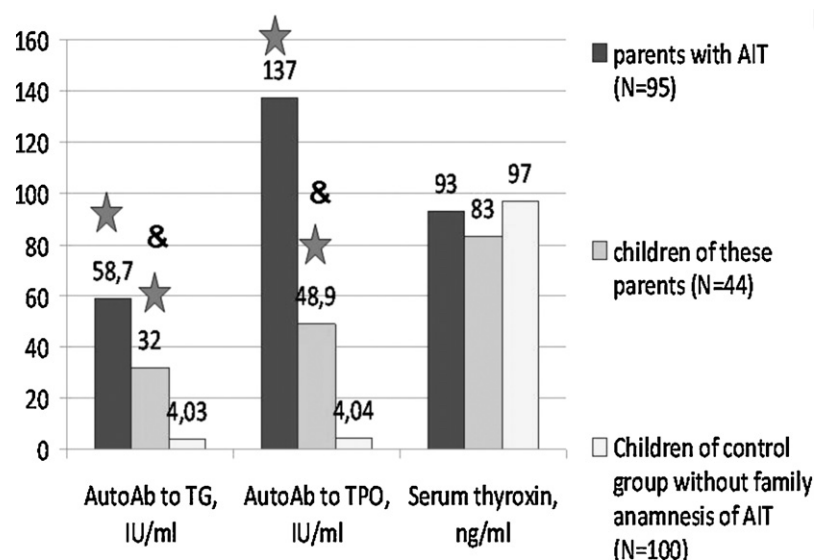


Fig. 4. Anti-thyroid autoimmunity and thyroid function in families with AIT and their so far healthy children and in controls. Asterisks mark statistically significant difference with controls.

accordance to statement of Metchnikoff. For full consistency of such mechanism, however, we should hypothesize the possibility of bidirectional Fc-receptor depending IgG transportation across placental barrier, as it was already proven for similar transfer via intestinal and urogenital barriers [32,33].

Maybe, spontaneous human chimerism is much more common phenomenon than it was supposed earlier. Retrospective analysis of our database of 3717 proven AIT patients has revealed among them – 8 cases of anamnestic blood group change (or Rh-factor change) – all of them medically documented with double check. Seven of the patients were multiparous ladies and one male, who experienced blood transfusions [34]. Blood group has been changed from AB for B (2 cases), 0 for B (1) or A for B (1), and Rh was changed from positive to negative (3 cases), or vice versa (1). We believe that this could result from chimerism or cell mosaics, which probably was key link of AIT pathogenesis in these patients. Interestingly, blood group 0 is predominating among AIT patients of our cohort much more obviously than in local population of St. Petersburg. We suggest that it is related to greater reaction of “nullers” toward microbial polysaccharide antigens and possible provocative role of germs for AIT [34].

Not only phenomena related to pregnancy, but also excessive emission of apoptotic garbage (including usually “hidden” intracellular tissue-specific antigens, e.g. TG and TPO from perishing thyrocytes) triggers off a rise in production of auto-antibodies of appropriate specificity [19]. In systemic autoimmune connective tissue diseases with presence of non-organ specific autoantibodies (systemic lupus erythematosus – SLE, scleroderma, rheumatoid arthritis etc.) one can observe high titers of autoantibodies against chromatin-associated and caryolemma-associated antigens (e.g. dsDNA, nucleohistones, or cardiolipin). But these particular antigens are most plentiful in apoptotic bodies, which contain chromatin and membrane material. Normally they are rapidly eliminated by tangible bodies’ macrophages, with minor fraction of debris only taken up by antigen-presenting dendritic cells. This supports minimal physiological level of natural autoimmunity. There are some evidences that the rate of withdrawal of apoptotic debris is decreased in SLE and related diseases; and appropriate function of CD68-positive tangible bodies’ macrophages in lymph nodes of these patients is weakened [35,36]. As a result, there is much greater uptake of apoptotic material by antigen-presenting elements, with survival signaling for appropriate autoreactive lymphocytes and much more intensive autoimmune response, exceeding the normal level. To a certain degree, this kind of an easily detected secondary autoimmune reaction should be considered as essentially adaptive, because these events tend to restore the disturbed homeodynamics, intensifying clearance in the organ involved and activating reparative processes. The latter can be proven by the fact that many auto-antibodies stimulate DNA synthesis, mitotic rates and cell proliferation [11,16–20,22]. Presumably, if the content of “cardiotropic”, “thyrotropic” or other “organotropic” auto-antibodies, as well as antinuclear ones, in blood sera of

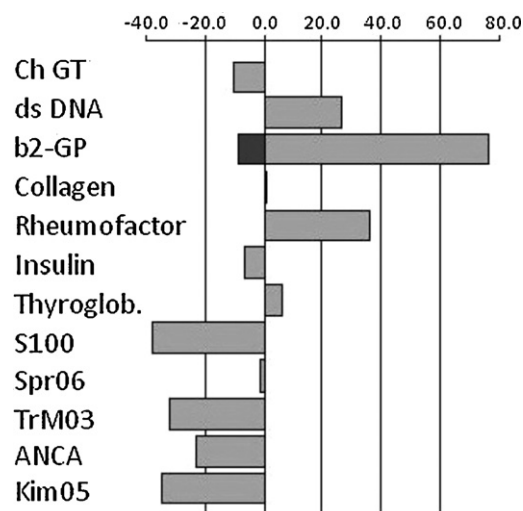


Fig. 5. Autoantibody level in patient B.C., investigated for anti- $\beta$ 2-glycoprotein I antibodies (b2-GP) by mono-kits “Orgentec”, Germany (black column) was shown below of population norm (average normal level from 3000 healthy donors accepted here and in all other diagrams as zero line). Autoantibodies of the same specificity and other serologic markers of antiphospholipid syndrome were revealed in the same sample by using of multiparametric kits (ELI-P-Complex Method), gray columns. All abbreviations decoded in the text.

investigated persons stay within the normal range – this result may indicate that apoptotic rates in heart, thyroid or other organs do not exceed physiological intensity and witness for the normal rate of clearance of apoptotic debris. On the other hand, in case of long-term increase of some organotropic auto-antibody production (for example, “pulmotropic”) one may suggest the presence of some pathological process in that organ (e.g., in lungs), even if there are still no evident clinical symptoms at the time of investigation. This process need not be of obligate immunopathological origin, like AIT. It can be any process, killing this organ’s cells. In our clinical diagnostic practice we have regularly observed that specific increase in serum level of “organotropic” auto-antibodies appears months or even years before the first clinical signs of different somatic diseases, formally not included into the group of autoimmune pathology [37]. It is the same for “non-organ specific”, or better to say “universal anti-apoptotic” autoantibodies: for example, in SLE and rheumatoid arthritis they are proven to appear years before overt clinical disease [38].

Here follow several clinical examples from our practice with brief case histories and appropriate spectra of autoantibodies, shown in Figs. 5–7. Because mono-tests for single particular kind of auto-Ab may not be always informative, we have elaborated and produced in our medical center multiparametric non-competitive solid phase ELISA assay kits for simultaneous determination of different auto-Ab(s) with the panels of autoantigens attached (ELI-test (Immunculus, Russia)) [19,39]. Level of certain auto-Ab(s) in an individual is evaluated in % compared to average one for population, last is taken for 100%. Algebraic total of deviations for

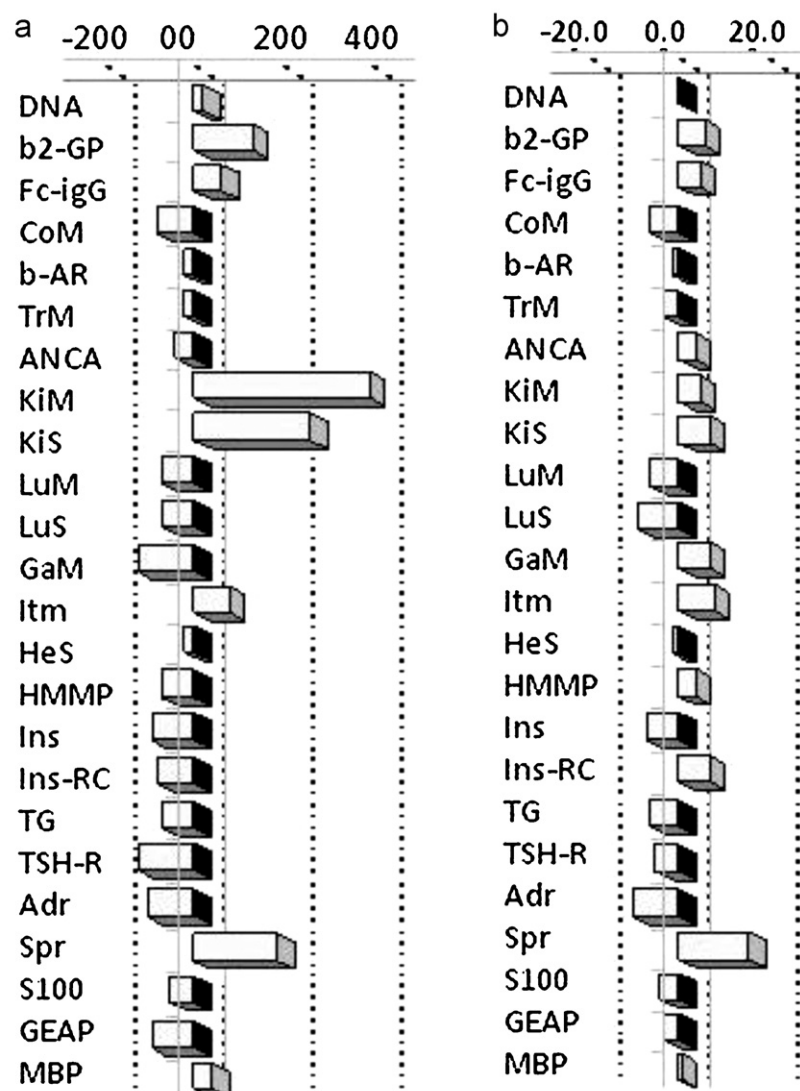


Fig. 6. (a) ELI-Viscero-Test data in patient M.N. before treatment, all abbreviations decoded in the text. (b) ELI-Viscero-Test data of the same person, M.N. 6 months after successful treatment of pyelonephritis and secondary arterial hypertension. All abbreviations decoded in the text.

all auto-Ab(s) controlled is referred to as index of *Average Individual Immune Reactivity (AIIR, which average level in population considered to be 0)*.

## 5. Clinical examples

**Example 1. Case History IMC-08-134, Patient B.C.** (29 y.o., female) (Fig. 5). Pregnancy 9–10 weeks, symptoms of threatening of miscarriage, elevated blood coagulation, echographic signs of placental blood flow disorder (by dopplerography). Leucopenia. Serum level of auto-Abs against beta<sub>2</sub>-Glycoprotein I (b2-GP) was below of population norm (data obtained by means of commercially available mono-kits “Orgentec”, Germany, shown with black column). Serological markers of anti-phospholipid syndrome were not revealed.

Results of multiparametric diagnostic investigation by non-competitive solid phase ELISA assay with ELI-P-Complex Kit (“Immunculus”, Russia) are shown with gray columns: auto-Abs against chorionic gonadotropin (Ch-GT): –51% from population norm; auto-Abs against double strand DNA (dsDNA): –31%; auto-Abs against b2-GP: –4%; auto-Abs against collagen: –45%; auto-Abs against Fc-fragment of IgG (Rheumofactor): –26%; auto-Abs against insulin: –49%; auto-Abs against thyroglobulin (Thyroglob., TG): –42%; auto-Abs against S100 protein (S100): –35%; auto-Abs against spermal antigen (SPR06): –46%; auto-Abs against small blood vessel antigen (ANCA): –63%; auto-Abs against platelet antigen (TrM03): –58%; auto-Abs against kidney antigen (Kim05): –64%.

AIIR = –45% (that is referred to as sign of prominent immune suppression); level of reactivity related to auto-Abs against beta<sub>2</sub>-Glycoprotein I is +76% compared to AIIR.

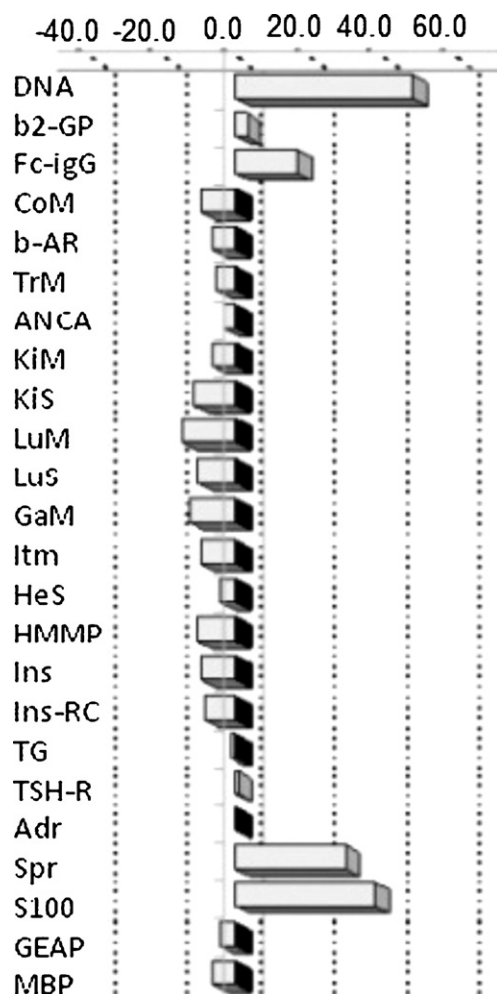


Fig. 7. ELI-Viscero-Test data of patient B.R. Ds.: prostate cancer in situ. All abbreviations decoded in the text.

**Conclusion:** prominent serological markers of anti-phospholipid syndrome were revealed with multiparametric kits Eli-test for analysis of individual profile of immune reactivity, but not with monoparametric kits (Fig. 5).

**Catamnestic clinical observations:** Miscarriage had happened at 12–13th weeks of pregnancy, most probably in relation to anti-phospholipid syndrome and placental blood flow disturbances.

**Example 2. Case History IMC-09-13, Patient M.N.** (48 y.o., male); complaints of unexplained weakness and indisposition; 4 episodes of abnormal elevation of blood pressure (up to 160/100) during the last 4–5 months.

**Results of multiparametric diagnostic investigation by ELI-Viscero-Test-24 Kit (“Immunculus”, Russia) (Fig. 6a and b):** auto-Abs against dsDNA: +1% to population norm; auto-Abs against b2-GP: +12%; auto-Abs against Fc-fragment of IgG (Fc-igG): +5%; auto-Abs against heart antigen beta2-adrenoreceptor (b-AR): -9%; auto-Abs against heart antigen Com: -3%; auto-Abs against platelets antigen TrM: -3%; auto-Abs against small blood vessel antigen ANCA: -5%; auto-Abs against kidney antigen Kim: +38%; auto-Abs

against kidney antigen Kis: +25%; auto-Abs against lung antigen Lus: -8%; auto-Abs against lung antigen Lum: -8%; auto-Abs against stomach wall antigen Gam: -14%; auto-Abs against intestinal wall antigen Itm: +7%; auto-Abs against liver antigen HMMP: -3%; auto-Abs against liver antigen Hes: -8%; auto-Abs against insulin (Ins): -11%; auto-Abs against insulin receptors (Ins-RC): -9%; auto-Abs against TSH receptor (TSH-R): -8%; auto-Abs against TG: -14%; auto-Abs against adrenal antigen Adr-QC: -12%; auto-Abs against prostate/spermal antigen SPR: +18%; auto-Abs against S100: -6%; Abs against astrocyte’s protein GFAP: -11%; Abs against myelin basic protein MBP: +3%.

Index AIIR = -1% (which is normal); prominently elevated immune reactivity against kidney antigens, and against prostate antigen was found (Fig. 6a). Additional investigation of urine revealed a moderate bacteriuria and plenty of white blood cells. Antibacterial treatment course with antibiotics and uroantiseptics in accordance with germ sensitivity was effective and bacteriuria/leucocyturia disappeared. Arterial blood pressure also normalized during 18 months regular observation did not reveal any episodes of arterial hypertension. After treatment Eli-test demonstrated tendency to normalization of autoantibodies spectrum with levels of anti-kidney and anti-prostate immunoreactivity decreased (Fig. 6b).

**Conclusion:** Early stage of secondary renal arterial hypertension was revealed; treatment of kidney infection was effective and resulted also in successful stopping at early stage of disease.

**Example 3. Case History IMC-08-201, Patient B.R.** (64 y.o., male); considered himself as healthy person, having no complaints.

**Results of multiparametric diagnostic investigation by ELI-Viscero-Test-24 Kit (“Immunculus”, Russia) (Fig. 7):** auto-Abs against dsDNA: +46%; auto-Abs against b2-GP: +1%; auto-Abs against Fc-igG: +15%; auto-Abs against heart antigen b-AR: -11%; auto-Abs against heart antigen Com: -8%; auto-Abs against platelet antigen TrM: -7%; auto-Abs against small blood vessel antigen ANCA: -5%; auto-Abs against kidney antigen Kim: -8%; auto-Abs against kidney antigen Kis: -13%; auto-Abs against lung antigen Lus: -16%; auto-Abs against lung antigen Lum: -12%; auto-Abs against stomach wall antigen Gam: -14%; auto-Abs against intestinal wall antigen Itm: -11%; auto-Abs against liver antigen HMMP: -6%; auto-Abs against liver antigen Hes: -12%; auto-Abs against Ins: -11%; auto-Abs against Ins-RC: -10%; auto-Abs against TSH-R: -3%; auto-Abs against TG: -1%; auto-Abs against adrenal antigen Adr-QC: -2%; auto-Abs against prostate/spermal antigen: SPR +28%; auto-Abs against S100: +36%; Abs against astrocyte’s protein GFAP: -6%; Abs against MBP: -8%.

Index AIIR = -2% (which is normal); prominently elevated immune reactivity against kidney cells, and against prostate antigen was found (Fig. 7). Additional investigation of prostate gland with positron emission tomography (PET) revealed abnormally intensive accumulation of glucose in



prostate; concentration of prostate-specific antigen in circulating blood was at high-normal level; later diagnosed prostate cancer in situ (confirmed by pathomorphological investigation of biopsy samples). Patient was successfully treated. Three years later any signs of malignancy were absent.

**Conclusion:** Early stage of prostate cancer was revealed; surgical treatment was effective.

## 6. Autoimmunomics in early diagnosis

Thus, elevation of the titers of autoAb(s) seems to be the earliest sign of incipient development of a latent disease, coming long before the overt insufficiency of appropriate organ. But, why is it so? Probably it may be related to an enormous excess of specialized cells in an organ (one of ways to achieve functional reliability) [22,23]. As a result, any *chronic* pathological process of almost every etiology will reach the stage of organ insufficiency only after a prolonged silent period, that is, not until the potential of regeneration is exceeded by long-lasting degenerative events with cell loss. Signs of functional insufficiency (such as peculiar biochemical changes and clinical manifestations) will only appear at an overt stage. Good example of that is progressive nephrosclerosis, which gives first functional and laboratory clinical manifestations of chronic renal failure after many years of unapparent course only, when more than half of nephrons has been already perished [22]. So, biochemical and pathophysiological deviations reflect perceptible functional failure of an organ relatively late. On the contrary, changes in auto-Ab level appear long before that, because they are related not to an organ's functional decline, but to abnormal activation of cell death events. For example, in large prospective study of the thyroid health in migrants from Chernobyl area [40] as well as in cohort study of adolescents and adults with marfanoid phenotype and Simpson-Page' syndrome [41] we have revealed elevated levels of anti-thyroid autoimmunity long before subsequent overt manifestation of AIT, hypothyroidism and metabolic syndrome. Potentially early pre-nosologic changes in any organ also may be early revealed by pathomorphological investigation of biopsy materials or cytological analysis of smears. However, unlike auto-antibody determination, this approach can hardly be applied for broad population screening (with little exclusion – like Pap smears in oncogynecology) and in some cases biopsy is not applicable physically (brain) or counterindicated clinically (AIT).

On the basis of our own clinical experience [19,37,39–41] and literature data [38,42] we believe that in the overwhelming majority of cases an abnormal rise of serum auto-Ab level with different antigen specificity is a secondary event (reflection), induced by some primary damage of an organ or a tissue. This kind of autoimmune reactions should be considered as *sanogenic* or beneficial in essence. However, autoimmune diseases, related to primary abnormal

elevation of auto-Ab production and/or excessive activation of autoreactive lymphoid clones are also highly spread. How can sanogenic (beneficial) autoimmune reactions be differentiated from the *pathogenic* (harmful) ones? It seems that primary autoimmune reactions (the ones not justified by real needs of an organism) in most cases are poorly regulated. Immune response may sometimes be inadequate in intensity, or incorrectly targeted, or badly driven, and in each case the result may be rather detrimental for an organism. All these situations, when immune response brings more harm than defense, are referred in Pathophysiology by the collection term “*allergy*” [22]. From a didactical point of view, we propose to use the term “*autoimmunity*” preferably in relation to physiological autoimmune processes. Adaptive secondary autoreactive responses (autoimmune) should be distinguished from “*autoallergic*” (mostly, primary) pathogenic immune reactions. We recommend using the term “*autoallergy*” for abnormal rise in production of auto-Ab(s) and autoreactive lymphocytes (provoked by viruses, bacteria, chemicals or other harmful factors, or related to disorders in the regulation of natural autoimmunity and non-conditioned by real needs of an organism).

## 7. Concluding remarks

1. Primary pathological processes in any organ usually lead to activation of cell death in populations and are reflected by secondary (adaptive, compensatory) rise of production and blood serum level of auto-Ab(s) with appropriate specificity. This reaction of the immune system is sanogenic and represents *autoimmunity*.
2. Much more rarely physicians can observe primary rise of auto-Ab production, mostly induced by different external stimuli or related to defects in autoimmunity control and not associated with to pre-existing disease of organ or tissue. Such situations are pathogenic in essence and may lead to *autoallergy* (autoallergic diseases). In our own practice correlation of occurrence of adaptive (secondary) autoimmune reactions and that of pathogenic (primary) autoallergic reactions is about 95/5.
3. Secondary quantitative changes in auto-Ab production may be detected months or years before the appearance of early clinical signs of a disease, and should be considered as a universal marker for virtually all chronic diseases, including those not entered today in the registry of autoallergic disorders. The analysis of quantitative changes in the content of natural auto-Ab may become an effective instrument for early pre-clinical and even pre-nosologic detection of pathological processes with different organic location and cellular targeting. In future, success in this area may result in revision of the main paradigm of medicine (DISEASE–TREATMENT), and transition to the new one (PROGNOSIS–PREVENTION), see also [38].

Of course, for this forecast to come true, we need not only diagnostic methods of autoimmunomics, but also effective and realizable algorithms of individualized prophylaxis adopted by health care practice. The problem of earliest pre-nosological diagnosis also has some bioethical aspects.

Reviewing the history of ideas in Immunology, we may notice that Metchnikoff shifted the accents in understanding the functions of immunity and emphasized its key role in *peace*, unlike other scientists, who stressed on its role in *war* [43]. It is quite symbolical that on May 30th 1909 he visited author of “*War and Peace*” and spent that day in conversations with L.N. Tolstoy.

Out of two thinkers, photographed together (Fig. 1), Tolstoy [44] wrote bitterly: “each human being has his own peculiarities, and has his peculiar, his own, new, complex disease; unknown to medicine . . . The field of medicine . . . still remains a wilderness. In comparison with the deeds of the organism itself, all that known medications can achieve is like one per mille”. Another, Metchnikoff [45] was a little bit more optimistic: “There is nothing unconceivable in the world, but a lot of it is not understood so far”.

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